

# MYLAN PHARMACEUTICALS INC

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March 16, 2004

Dockets Management Branch  
Food and Drug Administration (HFA-305)  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket 2004P-0061/CP1  
Comments of Mylan Pharmaceuticals Inc.

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. ("Mylan") submits this Comment in response to Jerome Stevens Pharmaceuticals, Inc.'s ("JSP") Citizen Petition No. 2004P-0061, filed on February 10, 2004 ("Petition"). The Petition requests the FDA to: (1) issue specific guidance for the submission of levothyroxine applications under § 505(j) of the Federal Food, Drug and Cosmetic Act ("FDCA") consistent with current guidance and requirements for levothyroxine products submitted under § 505(b)(2) of the FDCA; (2) not approve any ANDA for levothyroxine sodium that fails to conform to the standards for review established for 505(b)(2) applicants; and (3) immediately withdraw approval of the ANDA for levothyroxine submitted by Mylan if it did not meet the same standard for review applicable to 505(b)(2) applicants. Based on the information provided herein, Mylan does not believe the actions requested by JSP are warranted.

## **A. Additional Guidance for Submission of ANDAs for Levothyroxine is not necessary.**

Sections 505(j)(2)(A)(ii), (iii), and (iv) of the FDCA specify that an ANDA must contain information to show that the active ingredient, route of administration, dosage form, and strength are the same as the reference listed drug ("RLD") and that the drug is bioequivalent to the RLD. **The FDCA does not require an ANDA to contain the same information as a New Drug Application (NDA).** Under the Hatch-Waxman Amendments, the FDA issued specific regulations that govern bioequivalence determinations. The regulations at 21 CFR 320.23(b) state that "[t]wo products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions..."

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The conditions for approval of a bioequivalent, generic levothyroxine sodium drug product require that only a 600mcg single dose fasting *in vivo* bioequivalence study be conducted comparing the 300mcg strength of the test product to the RLD. Nevertheless, Mylan conducted three separate single dose fasting bioequivalence studies using the 75mcg, 125mcg, and 300mcg

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tablet strengths to cover the eleven strengths of levothyroxine sodium tablets available. The Division of Bioequivalence, Office of Generic Drugs, concluded that Mylan's levothyroxine sodium tablets met the FDA's bioequivalence criteria for AUC and Cmax (90% confidence interval within the limits of 80-125% based on log transformed baseline-corrected data). Bio-waivers for the remaining eight strengths were requested based on (1) acceptable bioequivalence studies of the 75mcg, 125mcg, and 300mcg strengths, (2) acceptable *in vitro* dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths. Furthermore, the FDA advised Mylan of the appropriate data needed for a levothyroxine ANDA which Mylan submitted in its application. Clearly, the FDA has established specific guidance for approval of levothyroxine ANDAs and, therefore, no further guidance is necessary.

**B. Mylan's ANDA for Levothyroxine Satisfies the Requisite Standard for Review.**

JSP's Petition requests the FDA to immediately withdraw approval of Mylan's ANDA for levothyroxine sodium tablets (equivalent to Unithroid®) because it may not have met the same standard for review which is applicable to 505(b)(2) applicants for levothyroxine sodium drug products. As discussed above, the FDCA does not require an ANDA to contain the same information as an NDA. The original ANDA submitted by Mylan on June 5, 2001 and approved June 5, 2002 satisfied all requirements for generic drug approval under section 505(j) of the FDCA.

**1. Content Uniformity and Potency**

In accordance with 21 CFR 314.94(a)(9), Mylan's ANDA contains the required chemistry, manufacturing and controls information to ensure that the finished drug product consistently meets the established requirements for identity, strength, quality, purity, and potency. Using the acceptance criteria recommended by FDA, homogeneity of powder blend is confirmed for every batch of levothyroxine sodium tablets that is manufactured. In addition, Mylan's manufacturing process includes the use of a potency factor calculation to ensure that the finished product is formulated to contain 100% of label claim of Levothyroxine Sodium, USP. Since approval of Mylan's ANDA for Levothyroxine Sodium Tablets on June 5, 2002, Mylan has released 80 batches of drug product which encompass all eleven strengths. The content uniformity of the 80 batches has a mean of means of 100.5% with a range of RSDs from 0.7 to 2.9%. An evaluation of the content uniformity shows exceptional product homogeneity in that a relative standard deviation of 1.5% for a ten-tablet assessment is considered typical. Furthermore, the range of RSDs demonstrates that Mylan's product is consistent in uniformity from batch to batch. The potency of the 80 batches has a mean of 99.4% with an RSD of 1.7%. A comparison of the potency test results with reference to the corresponding uniformity mean results generally show agreement within 1%. These data demonstrate that Mylan's generic levothyroxine sodium drug product is also consistent in potency from lot to lot.

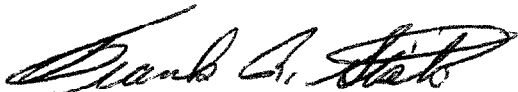
**2. Stability**

In accordance with 21 CFR 314.94(a)(9), Mylan's original application complied with the requirements for providing drug product stability data. ANDA applicants are not required to submit the same stability information as NDA applicants because the stability data requirements

for ANDAs are determined in part by the existence of a significant body of information for the dosage form and the existence of an approved application for the particular dosage form. Mylan's generic product demonstrates 24 months of acceptable stability at the recommended ICH long term storage condition of 25°C and 60% RH. Mylan's ANDA also contained stability data generated at the other ICH recommended stability challenge conditions for ANDAs. These studies, completed for all strengths, included 3 months of extreme challenge at 40°C and 75% RH and 12 months of intermediate challenge at 30°C and 60% RH. The data demonstrated that Mylan's generic levothyroxine sodium tablets are stable under real time room temperature studies for two years. Since approval of Mylan's ANDA for levothyroxine sodium tablets on June 5, 2002, Mylan has manufactured three production scale batches for each strength as part of the post approval validation commitment to the FDA. A review of the data from the current stability program for commercial production lots (a minimum of 3 for each product strength, 36 total), representing 12 months of test data at 25°C and 60% RH, supports product stability in that potency and related compounds remain within approved specifications and do not significantly deviate from those test results acquired at time of product release.

In conclusion, therapeutic equivalence (bioequivalence and pharmaceutical equivalence) of Mylan's generic levothyroxine sodium tablets to Unithroid® has been demonstrated. In addition, the frequency of adverse events reported for Mylan's levothyroxine sodium tablets (14 months post-launch) is less than half the frequency of adverse events reported for all other brands of levothyroxine sodium tablets (evaluated 3 years prior to launch), which confirms the safety profile for Mylan's product [Sources: IMS National Prescription Audit; and Data Extract from CDER's Adverse Event Reporting System (AERS)]. The significant body of potency, content uniformity, and stability data demonstrates Mylan's ability to consistently produce a homogeneously potent and stable generic levothyroxine sodium tablet dosage form under a controlled manufacturing process. Most importantly, JSP in its Petition does not present any new evidence which questions the effectiveness and safety of Mylan's ANDA for levothyroxine. Without any new evidence, the FDA has no obligation to review the approval status of Mylan's ANDA for levothyroxine sodium tablets. Mylan, therefore, respectfully requests the FDA to immediately deny JSP's Petition.

Respectfully submitted,



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